CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-031/S-025

Name:	Paxil Tablets (paroxetine hydrochloride)
Sponsor:	SmithKline Beecham Pharmaceuticals
Approval Date:	May 17, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-025

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Approvable Letter(s)	X
Final Printed Labeling	
Medical Review(s)	
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Administrative Document(s)	
Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-025

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 20-031/S-025

MAY 17 2000

SmithKline Beecham
Attention: Deborah E. Zuber, R.Ph.
Assistant Director, Drug Regulatory Affairs
1250 S. Collegeville Road, P.O. Box 5089
Collegeville, PA 19426-0989

Dear Ms. Zuber:

Please refer to your supplemental new drug application dated March 12, 1999, received March 15, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil (paroxetine hydrochloride) Tablets.

We acknowledge receipt of your submission dated November 19, 1999. Your submission of November 19, 1999 constituted a complete response to our September 19, 1999 action letter.

This supplemental new drug application provides for an alternate site for all stages of drug substance manufacture at your Cork, UK facility.

We have completed the review of this supplemental application and it is approved.

Reference is also made to a conference call dated May 17, 2000, between the Agency and representatives of SmithKline Beecham to discuss the [ ] produced in the drug substance manufactured at both the Cork, UK and Irvive, UK manufacturing establishments.

We acknowledge your commitment, from our May 17, 2000 conference call, to submit a prior approval supplement to modify the [ ] [ ] [ ]. This supplemental application would need to contain supporting pharmacology/toxicology data as well as appropriate chemistry and manufacturing data.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

5/10/00

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-031
HFD-120/Div. Files
HFD-120/P.David
HFD-120/R.Seevers/R.Lostritto
HFD-095/DDMS-IMT
HFD-810/DNDC Division Director
DISTRICT OFFICE

Drafted by: /May 17, 2000
Initialed by:
final:
filename:

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-025

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 20-031/S-025

SmithKline Beecham
Attention: Deborah E. Zuber, R.Ph.
Assistant Director
1250 S. Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

SEP 15 1999

Dear Ms. Zuber:

Please refer to your supplemental new drug application dated March 12, 1999, received March 15, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil® (paroxetine hydrochloride) Tablets.

We acknowledge receipt of your amendment dated August 19, 1999.

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

This supplement proposes the following change(s): An alternate site of drug substance synthesis stages [ ] at your Cork facility to serve as an alternate site for the full manufacture of paroxetine hydrochloride. The supplement also provides for changes in tests and specifications at your Cork facility. We note that some of these changes in tests and specifications were disclosed in your original supplement. However, full disclosure of all of these changes was submitted on August 19, 1999, at the request of the Agency.

Your submission stated April 12, 1999 as the implementation date for the change(s).

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. [ ]

2. [ ]

3. [redacted]

a) [redacted]

b) [redacted]

Please note that until this supplement is approved, you may not market any batches of drug product made using drug substance from the proposed Cork site.

Additionally, we request that all future supplemental applications state, within the body of the cover letter, all proposed changes which the supplemental application provides for.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, contact Paul David, R.Ph., Regulatory Management Officer, at (301) 594-5530.

Sincerely,

9/15/99

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products (HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-031
HFD-120/Div. Files
HFD-120/P.David
HFD-120/R.Lostritto RR 9/15/99
HFD-120/R.Seevers
DISTRICT OFFICE

Drafted by: RTL/September 15, 1999
Initialed by:
final:
filename: N20031.L25

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-025

CHEMISTRY REVIEW(S)

MAY 17 2000

CHEMIST'S REVIEW

1. ORGANIZATION HFD-120 DNDP	2. NDA NUMBER 20-031
3. NAME AND ADDRESS OF APPLICANT *(City and State)* SmithKline Beecham Pharmaceuticals, Collegeville, PA	4. AF NUMBER
	5. SUPPLEMENT (S) NUMBER(S) DATES(S) SCM-025 (AC) Amendment 11/22/99 (CDER Date) (subject of this review)
6. NAME OF DRUG Paxil® Tablets	7. NONPROPRIETARY NAME paroxetine hydrochloride
8. SUPPLEMENT PROVIDES FOR: an alternate site of drug substance synthesis stages [ ] at SB's Cork Ireland facility to serve as an alternate site of manufacture for all stages of drug substance manufacture. The subject of this review (AC amendment dated 11/22/99) constitutes a full response to the 9/15/99 Agency approvable letter.	9. AMENDMENTS DATES 8/19/99 (letter date) 8/20/99 (stamp date) Provides a list of other changes which were not disclosed in the original submission.
10. PHARMACOLOGICAL CATEGORY treatment of depression	11. HOW DISPENSED RX X OTC _____
13. DOSAGE FORM(S) film coated IR tablets	14. POTENCY .
15. CHEMICAL NAME AND STRUCTURE see 1996 USAN page	12. RELATED IND/NDA/DMF SCM-025 (original) dated 3/15/99 (see CR#1 and Approvable action letter dated 9/15/99
	16. RECORDS AND REPORTS CURRENT YES_____NO_____ REVIEWED YES_____NO_____

17. COMMENTS

cc:
Orig. NDA # 20-031
HFD-120/Div. File
HFD-120/RLostritto
HFD-120/RSeevers
HFD-120/PDavid
R/D Init. by: RTL 5/17/00
F/T by: RTLostritto
doc # n20031.f25

18. CONCLUSIONS AND RECOMMENDATIONS. This supplement may be **approved.** The applicant provided adequate release and stability data to support the proposed site change. The applicant commits to evaluate release and stability purity data and update the specification via a prior approval supplement as described herein. **See attached Draft Letter Comments.**

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Richard T. Lostritto, Ph.D.	RTLostritto 5/17/00	5/17/00

DISTRIBUTION ORIGINAL JACKET ___ DIVISION FILE ___ REVIEWER ___ CSO ___ TEAM LEADER ___

Redacted 6 page(s)

of trade secret and/or

confidential commercial

information from

Chemistry Review #2

S-025

SEP 15 1999

CHEMIST'S REVIEW	1. ORGANIZATION HFD-120 DNDP	2. NDA NUMBER 20-031
3. NAME AND ADDRESS OF APPLICANT *(City and State)* SmithKline Beecham Pharmaceuticals, Collegeville, PA		4. AF NUMBER
		5. SUPPLEMENT (S) NUMBER(S) DATES(S) SCM-025CBE 3/15/99 (CDER Date) (subject of this review)
6. NAME OF DRUG Paxil® Tablets	7. NONPROPRIETARY NAME paroxetine hydrochloride	
8. SUPPLEMENT PROVIDES FOR: an alternate site of drug substance synthesis stages [ ] at SB's Cork Ireland facility to serve as an alternate site of manufacture for all stages of drug substance manufacture. The supplement also provides for changes not disclosed in the original supplement and which were provided in the requested 8/19/99 amendment.		9. AMENDMENTS DATES 8/19/99 (letter date) 8/20/99 (stamp date) Provides a list of other changes which are not disclosed in the original submission.
10. PHARMACOLOGICAL CATEGORY treatment of depression	11. HOW DISPENSED RX X OTC ____	12. RELATED IND/NDA/DMF
13. DOSAGE FORM(S) film coated IR tablets	14. POTENCY .	
15. CHEMICAL NAME AND STRUCTURE see 1996 USAN page		16. RECORDS AND REPORTS CURRENT YES____NO____ REVIEWED YES____NO____

17. COMMENTS

cc:
Orig. NDA # 20-031
HFD-120/Div. File
HFD-120/RLostritto
HFD-120/RSeevers
HFD-120/PDavid
R/D Init. by: RAS
F/T by: RTLostritto
doc # n20031.s25

18. CONCLUSIONS AND RECOMMENDATIONS. This supplement is **APPROVABLE**. The applicant needs to provide assurance that essential testing for residual solvents was performed. The applicant also needs to address discrepancies in impurity profiles and out of specification stability results for the drug substance. EER acceptable 9/14/99. **See attached Draft Letter Comments.**

19. REVIEWER

NAME	SIGNATURE.	DATE COMPLETED
Richard T. Lostritto, Ph.D.	9/15/99	9/14/99

DISTRIBUTION ORIGINAL JACKET ___ DIVISION FILE ___ REVIEWER ___ CSO ___ TEAM LEADER ___

Redacted 7 page(s)

of trade secret and/or

confidential commercial

information from

Chemistry Review #1

S-025

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-031/S-025

CORRESPONDENCE

SmithKline Beecham
Pharmaceuticals

NDA SUPP AMEND
(AC)
SCM-025

November 19, 1999

ORIGINAL

NDA 20-031/S-025
Paxil® (paroxetine hydrochloride, hemihydrate) Tablets

Russell Katz, M.D., Director
Division of Neuropharmacologic
Drug Products (HFN-120, Room 10B-45)
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
NOV 22 1999
RECEIVED HFD-120

Dear Dr. Katz:

Re: Amendment to S-025/Response to FDA Request for Additional Information

Dear Dr. Katz:

Reference is made to the New Drug Application NDA 20-031 for Paxil® (paroxetine hydrochloride) Tablets and to the Approvable letter dated September 15, 1999 for Supplement S-025.

The Supplement S-025 provides for SmithKline Beecham's Cork, Ireland facility as an alternate site for full manufacture of paroxetine hydrochloride, hemihydrate. The supplement also provides for changes in the tests and specifications at the Cork facility. Before the supplement could be approved, FDA requested SmithKline Beecham address three (3) comments.

Responses to these comments are provided in this submission as described below.

"1. [redacted]

F:\paxil\Tablets_20031\Amendment to S-025.doc\1

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989. Telephone (610) 917 7000. Fax (610) 917 7707.

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

Correspondence (Re: Amendment to S-025 11/19/99)

S-025

Please do not hesitate to contact me regarding additional questions or comments at (610) 917-6884 or FAX at (610) 917-4704.

Sincerely,

Deborah E. Zuber

Deborah E, Zuber, R.Ph.
Assistant Director
N.A. Regulatory Affairs

SmithKline Beecham
Pharmaceuticals

August 19, 1999

NDA 20-031; Supplement S-025
Paxil® (paroxetine hydrochloride) Tablets

Russell G. Katz, M.D., Acting Director
Division of Neuropharmacologic Drug Products (HFD-120, Room 4049)
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: Amendment to Special Supplement "Changes Being Effected" S-025

Dear Dr. Katz:

Reference is made to NDA 20-031 for Paxil® (paroxetine hydrochloride) Tablets, 10 mg, 20 mg, 30 mg, and 40 mg, and to the special supplement "Changes Being Effected" Supplement S-025, submitted on March 12, 1999, for the manufacture of paroxetine hydrochloride, hemihydrate, drug substance stages [ ] at the SmithKline Beecham Cork, Ireland facility. This submission is being provided at the request of Mr. Paul David, FDA Regulatory Project Manager, on August 17, 1999 in a telephone conversation. Mr. David requested SmithKline Beecham to confirm that there are no changes to the drug substance specifications and to the synthetic process in Stages [ ] as compared to the currently approved drug substance synthesis at the SmithKline Beecham Irvine, Scotland, UK, facility.

Upon reviewing the Supplement S-025, it is confirmed that the synthetic drug substance process for Stages [ ] are equivalent to the Irvine synthetic process. Cork manufactured an identical Stage [ ] process to Irvine's. The following are minor differences with some of these being related to site specific operations .

1. [ ]

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989. Telephone (610) 917 7000. Fax (610) 917 7707.

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

Correspondence (Re: Amendment to Special Suppl.- 8/19/99)

S-025

4. [redacted]

If you should have any additional comments or questions concerning this submission, please do not hesitate to contact me at (610) 917-6884.

Sincerely,

Deborah E. Zuber

Deborah E. Zuber, R.Ph.
Assistant Director
Regulatory Affairs, North America

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-031/S-025

Smithkline Beecham Pharmaceuticals
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0989

MAR 23 1999

Attention: Deborah E. Zuber, Assistant Director

Dear Ms. Zuber:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Paxil Tablets

NDA Number: 20-031

Supplement Number: S-025

Date of Supplement: March 12, 1999

Date of Receipt: March 15, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on May 14, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-031/025
HFD-120/Div. Files
HFD-120/CSO/David

filename: C:\WPWIN61\TEMPLATE\FDA\20-031.025

SUPPLEMENT ACKNOWLEDGEMENT

SmithKline Beecham
Pharmaceuticals

March 12, 1999 ORIGINAL

CENTER FOR DRUG EVALUATION
AND RESEARCH

MAR 15 1999

RECEIVED HFD-120

NDA SUPPLEMENT

NDA NO. 20-031 REF NO. SCnl-025
NDA SUPPL FOR Manufacturing

NDA 20-031
Paxil® (paroxetine hydrochloride) Tablets

Russell Katz, M.D., Acting Director
Division of Neuropharmacological
Drug Products (HFN-120, Room 10B-45)
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: Special Supplement - Changes Being Effected
Paroxetine Hydrochloride Drug Substance –
Manufacturing Site Transfer Stages [ ]

Dear Dr Katz:

Reference is made to SmithKline Beecham's approved New Drug Application for Paxil® (paroxetine hydrochloride) Tablets, NDA 20-031. Currently paroxetine hydrochloride drug substance Stages [ ] are being manufactured at SB's Cork, Ireland facility and Stages [ ] at SB's Irvine, Scotland facility. This supplement is being provided for the registration of SB's Cork, Ireland facility as an alternate site of manufacture for all stages of paroxetine hydrochloride. This submission provides the following -

- the process description reflecting the manufacturing of Stages [ ] at SB's Cork, Ireland facility. The [ ] range has been added for the Cork, Ireland facility and in the recent 1998 Paxil Annual Report, Stages [ ] [ ] at the Irvine facility was also changed to reflect the [ ] range.

F:\paxil\Tablets_20031\CorkIrv.DOC\1

- the updated specifications and methods for the solvents and intermediates used in the method of manufacture of paroxetine hydrochloride. Also included is the manufacturing orders for paroxetine hydrochloride Stages [redacted].

- the representative equipment list, packaging component specifications and container closure labels.

- the comparative batch analysis and detailed impurity profile between the Cork, Ireland and Irvine, Scotland facility. Also included is stability data for drug substance produced at the Cork, Ireland facility.

In conclusion, final drug substance manufactured by SB's Cork, Ireland facility demonstrates that final drug substance is equivalent quality to drug substance produced at SB's Irvine facility and meets the currently approved NDA drug substance specifications.

The changes described above will be implemented within 30 days of this submission. The first 3 commercial batches produced from the Cork, Ireland facility (Stages [redacted]) will be placed on stability and the data reported in the Annual Report. In addition, Drug Product will be manufactured with Cork drug substance at Cidra and the stability data will be reported in the Annual Report.

If you have any questions concerning this submission, please do not hesitate to contact me at (610) 917-6582.

Sincerely,

Deborah Zuber

Deborah Zuber
Assistant Director
Regulatory Affairs, North America